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SYNTHESIS OF AMINOARYLBORONIC ESTERS AND SUBSTITUTED ANILINES FROM ARENES VIA CATALYTIC C-H ACTIVATION/BORYLATION/AMINATION AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Patent Application No. 60/397,369, filed July 19, 2002.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable

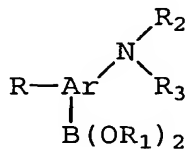
Reference to a "Computer Listing Appendix submitted on a Compact Disc"

Not Applicable.

BACKGROUND OF THE INVENTION

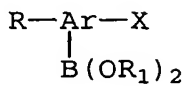
(1) Field of the Invention

The present invention relates to a process for synthesizing aminoarylboronic esters of the general formula



wherein R, R_2, and R_3 are each independently an alkyl, aryl, vinyl, alkoxy, carboxylic esters, amides, or halogen; Ar is any variety of phenyl, naphthyl,

anthracyl, heteroaryl; and R_1 is alkyl, hydrogen, or aryl. The aminoarylboronic esters are produced via the metal-catalyzed coupling of arylboronic esters of the general formula



wherein R and R_1 are any non-interfering group and X is chloro, bromo, iodo, triflates, or nonaflates to amines (primary and secondary). In particular, the present invention provides a process for the synthesis of the aminoarylboronic esters via a step-wise or tandem process in which one catalytic event is a metal-catalyzed borylation and the other catalytic event is a metal-catalyzed amination.

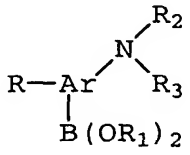
(2) Description of Related Art

There is no single method established for the synthesis of aminoarylboronic esters in the prior art. The most common method involves the derivatization of 3-amino-phenylboronic acid (*See* for a recent example; Gravel et al., J. Org. Chem. 67: 3 (2002)), which in turn was originally synthesized from 3-bromonitrobenzene via (i) grignard formation, (ii) reaction with a alkylborate followed by hydrolysis, (iii) and reduction of the nitro group (*See*, Bean and Johnson, J. Am. Chem. Soc. 54: 4415 (1932)).

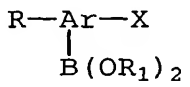
Therefore, there remains a need for a process for synthesizing aminoarylboronic esters and substituted anilines from arenes that is safer and less laborious than the prior art methods.

SUMMARY OF THE INVENTION

The present invention provides a process for synthesizing aminoarylboronic esters of the general formula



wherein R, R_2, and R_3 are each an alkyl, aryl, vinyl, alkoxy, carboxylic esters, amides, or halogen; Ar is any variety of phenyl, naphthyl, anthracyl, heteroaryl; and R_1 is alkyl, hydrogen, or aryl. The aminoarylboronic esters are produced via the metal-catalyzed coupling of arylboronic esters of the general formula



wherein R and R_1 are any non-interfering group and X is chloro, bromo, iodo, triflates, or nonaflates to amines (primary and secondary). In particular, the present invention provides a process for the synthesis of the aminoarylboronic esters via a step-wise or tandem process in which one catalytic event is a metal-catalyzed borylation and the other catalytic event is a metal-catalyzed amination.

Therefore, the present invention provides a process for producing an aminoarylboronic ester which comprises (a) reacting an aryl compound with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a

catalytically effective amount of an iridium or rhodium complex with three or more substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands, preferably under anhydrous conditions, to produce an arylboronic ester; and (b) aminating the arylboronic ester with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester.

The present invention further provides a process for producing an aminoarylboronic ester which comprises (a) reacting in a reaction vessel an aryl compound with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a catalytically effective amount of an iridium or rhodium complex with three or more substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands, preferably under anhydrous conditions, to produce an arylboronic ester; and (b) aminating the arylboronic ester formed in the reaction vessel with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester.

The present invention further provides a process for C-N coupling an aryl halide to an aminoarylboronic ester via the amine functionality of the aminoarylboronic ester which comprises (a) reacting in a reaction vessel an aryl compound with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a catalytically effective amount of an iridium or rhodium complex with three or more substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands, preferably under anhydrous conditions, to produce an arylboronic ester; (b) aminating the arylboronic ester formed in the reaction vessel with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester; and (c) reacting the aminoarylboronic ester with the aryl halide in the presence of a palladium metal catalyst complex in the presence of water to couple the aryl halide to the aminoarylboronic ester.

The present invention further provides a process for C-C coupling an aryl halide to an aminoarylboronic ester via the borane functionality of the aminoarylboronic ester which comprises (a) reacting in a reaction vessel an aryl compound with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a catalytically effective amount of an iridium or

rhodium complex with three or more substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands, preferably under anhydrous conditions, to produce an arylboronic ester; (b) aminating the arylboronic ester formed in the reaction vessel with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester; and (c) reacting the aminoarylboronic ester with the aryl halide in the presence of a palladium metal catalyst complex in the presence of water to couple the aryl halide to the aminoarylboronic ester.

The present invention further provides a process for producing an aminoarylboronic ester which comprises reacting an arylboronic ester with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester.

The present invention further provides a process for producing a substituted phenol amine which comprises (a) reacting in a reaction vessel an aryl compound with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a catalytically effective amount of an iridium or rhodium complex with three or more

substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands under anhydrous conditions to produce an arylboronic ester; (b) aminating the arylboronic ester formed in the reaction vessel with an organic compound containing an amine moiety in the presence of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce an aminoarylboronic ester; and (c) oxidizing the aminoarylboronic ester with a hydrogenating oxidizing compound to produce the substituted phenol amine.

In a further embodiment of the above processes, iridium complex is selected from the group consisting of $((COD)Ir(OCH_3))_2$, $(Cp^*)Ir(H)_2(Me_3P)$, $(Cp^*)Ir(H)(BPin)(Me_3P)$, $(Cp^*)Ir(H)(C_6H_5)(Me_3P)$, $(Ind)Ir(COD)$, $(Ind)Ir(dppe)$, $(MesH)Ir(BPin)(B(OR)_2)_2$, $((R_1)_3P)_3Ir(B(OR_2)_2)_3$, $(R_1)_2P)_2Ir(BPin)_3$, $(((R_1)_2P)_3Ir((R_2O)_2B)_3)_2$, $((R_1)_3P)_4Ir(BPin)$, $((R_1)_3P)_2Ir(BPin)_3$, $(MesH)Ir(BPin)_3$, and $(IrCl(COD))_2$, $(PMe_3)_2IrH_5$, $((R_1)_3P)_2IrH_5$, and $((R)_3P)_2IrH_x(B(OR_2)_2)_{5-x}$ where x is 0-4, wherein Cp* is 1,2,3,4,5-pentamethylcyclopentadienyl, BPin is pinacolborane, Me is methyl, H is hydrogen, P is phosphorus, Ind is indenyl, COD is 1,5-cyclooctadiene, MesH is mesitylene, and wherein R, R_1, and R_2 are hydrogen, linear or branched alkyl containing 1 to 8 carbons, aryl, or a carbon in a cyclic structure.

In a further embodiment of the above

processes, the iridium complex is (Ind)Ir(COD) or $((COD)Ir(OCH_3))_2$ wherein Ind is indenyl and COD is 1,5-cyclooctadiene.

In a further embodiment of the above processes, the organic ligand is a phosphorus organic ligand selected from the group consisting of trimethyl phosphine (PMe_3), 1,2-bis(dimethylphosphino)ethane (dmpe), and 1,2-bis(diphenylphosphino)ethane (dppe). In other embodiments, the organic ligand is a nitrogen ligand selected from the group consisting of 2,2'-dipyridyl and 4,4'-di-tert-butyl-2,2'-dipyridyl.

In a further embodiment of the above processes, the borane is pinacolborane (BPin).

In a further embodiment of the above processes, the metal catalyst is palladium.

In a further embodiment of the above processes, the metal catalyst complex is selected from $Pd(PPh_3)_4$, $Pd_2(dba)_3/P(^tBu)_3$, $PdCl_2(dppf)$, and $Pd(OAc)_2/Cy_3P$ wherein P is phosphorus and Ph is phenyl, dba is dibenzylideneacetone, ^tBu is *tert*-butyl, dppf is diphenylphosphinoferrocene.

In a further embodiment of the above processes, wherein the aryl compound has the formula (R)Ar(X), the arylboronic ester has the formula $(R)Ar(X)B(OR_1)_2$, and the aminoarylboronic ester has the formula $(R)Ar(NR_2R_3)B(OR_1)_2$ wherein R, R_2, and R_3 are each any non-interfering group, preferably a group selected from the group consisting of alkyl, aryl, vinyl, alkoxy, carboxylic esters, amides, and halogen; Ar is selected from the group consisting of phenyl, naphthyl, anthracyl, and heteroaryl; X is a halogen or pseudohalogen preferably selected from the group

consisting of chloro, bromo, iodo, triflates, and nonaflates; and R_1 is any non-interfering group, preferably a group selected from the group consisting of alkyl, hydrogen, and aryl.

In particular embodiments of the above borylation reactions, the molar ratio of the aryl compound to the borane is between about 10 to 1 and 1 to 10, preferably the molar ratio of the aryl compound to borane is about 1 to 2.

In particular embodiments of the above amination reactions, the reactions include a base and a second organic ligand. In some embodiments the base is K_3PO_4 and in some embodiments, the second organic ligand is P*t*Bu$_3$, 2(N,N'-dimethylamino)-2'-dicyclohexylphosphino-1,1'-biphenyl, 2-dicyclohexylphosphino-1,1'-biphenyl, and 2-di-*t*-butylphosphino-1,1'-biphenyl.

In further embodiments of the above processes for producing the aminoarylboronic ester, the aminoarylboronic ester which is produced is then reacted with an oxidizing compound to replace the boronic ester group with an oxygen.

In further embodiments of the process for producing substituted phenols from an aryl compound, the oxidizing compound is a peroxy compound selected from the group consisting of peroxymonosulfuric acid and salts thereof. In a further embodiment, the oxidizing compound is taken from the group consisting of organic peroxides and salts thereof. In a further embodiment of the above processes, the oxidizing agent is hydrogen peroxide. In a further embodiment of the above processes, the oxidizing compound is an alkali

metal peroxymonosulfate, preferably potassium peroxymonosulfate, most preferably $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

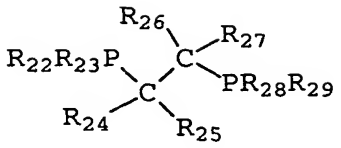
OBJECTS

It is an object of the present invention to provide a process for the synthesis of aminoarylboronic esters and substituted anilines from arenes.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 shows the formulas for precatalysts **1** to **15**. Cp* is 1,2,3,4,5-methylcyclopentadienyl, BPin is pinacolborane, Me is methyl, H is hydrogen, P is phosphorus, Ind is indenyl, COD is 1,5-cyclooctadiene, MesH is mesitylene, and wherein R, R_1, and R_2 are each selected from the group consisting of hydrogen, linear or branched alkyl containing 1 to 8 carbons, aryl, and a carbon in a cyclic structure.

Figure 2 shows the formulas for precatalysts **16** to **27**. Y_4, Y_5, and Y_6 are each selected from the group consisting of hydrogen, halide, alkyl, aryl, alkoxide ($-O(R_{11})$), and amide ($-N(R_{12})(R_{13})$) wherein R_{11}, R_{12}, and R_{13} are each selected from the group consisting of hydrogen, linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, and a carbon in a cyclic structure; R_{14}, R_{15}, and R_{16} are each selected from the group consisting of hydrogen, linear alkyl, branched alkyl, and a carbon in a cyclic structure; (PY_7P) is $R_{18}R_{19}P-Y_7-PR_{20}R_{21}$ wherein R_{18}, R_{19}, R_{20}, and R_{21} are each selected from the group consisting of hydrogen, linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, and a carbon in a cyclic structure, and Y_7 is a chain containing 1 to 12 carbons; (P^P) is of the formula



wherein R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each selected from the group consisting of alkyl chains, carbocyclic rings, and aryl groups; and BY is a boron moiety.

DETAILED DESCRIPTION OF THE INVENTION

All patents, patent applications, provisional patent applications, government publications, government regulations, and literature references cited in this specification are hereby incorporated herein by reference in their entirety. In case of conflict, the present description, including definitions, will control.

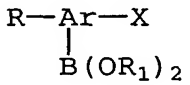
The present invention provides a process for producing an aminoarylboronic ester which comprises reacting an aryl compound which is a ring-substituted arene wherein at least one ring substituent is a halogen (aryl halide) or pseudohalogen (e.g., nonaflates and triflates), with a borane selected from the group consisting of a borane with a B-H, B-B, and B-Si bond in the presence of a catalytically effective amount of an iridium or rhodium complex with three or more substituents, and an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands, preferably under anhydrous conditions, to produce an arylboronic ester; and then aminating the arylboronic ester with an organic compound containing an amine in the presence

of a catalytically effective amount of a metal catalyst complex under anhydrous conditions wherein the organic compound is coupled to the aryl group of the arylboronic ester compound to produce the aminoarylboronic ester. The process further includes embodiments wherein the aryl compound is aminated as above and then borylated as above. The process further includes reactions wherein the aryl compound is an aminoaryl compound which is borylated as above.

The process can be performed as a single "one-pot" reaction in a single reaction vessel. Thus, the advantages of the process of the present invention is that it provides direct access to aminoarylboronic acids and esters without need for intermediate purification, isolation, and characterization; thus saving time, expense, money, and reducing hazardous waste, and allows access to aminoarylboronic acids and esters which were previously unknown or difficult/impossible to synthesize using traditional methods. The process of the present invention is particularly useful for pharmaceutical research, commodity chemical producers, specialty chemical manufacturers, and university-based research efforts.

In the first reaction, the B-C bond-forming reaction between a borane and an sp^2-hybridized C-H bond of a ring-substituted arene in which at least one of the ring substituents is a halogen or pseudohalogen (aryl compound) to produce an arylboronic ester is catalyzed by a catalyst comprising Ir or Rh in a complex with three or more substituents, preferably excluding hydrogen as a substituent, bonded to the Ir or Rh. In a further embodiment, the reaction includes

an organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands. For example, phosphorus organic ligands; nitrogen organic ligands such as pyridine, bipyridines (bpy), trigonal bipyridine (tbpy), and the like; and, organic amines, imines, nitrogen heterocycles, ethers, and the like. Preferably, the ligand to catalyst is in a molar ratio between about 1 to 3 and 3 to 1, preferably 1 to 1, wherein the organic ligand is at least in part bonded to the iridium or rhodium. In general, the ring-substituted arene (aryl compound) has the formula R-Ar-X and the arylboronic ester has the formula



wherein R is any non-interfering group, preferably selected from the group consisting of alkyl, aryl, vinyl, alkoxy, carboxylic esters, amides, cyclic, heteroaryl, heterocyclic, substituted variants thereof, and hydrogen; Ar is any variety of aryl, phenyl, naphthyl, anthracyl, and heteroaryl, and substituted variants thereof; R_1 is any non-interfering group, preferably selected from the group consisting of alkyl, aryl, heteroaryl, and substituted variants thereof, and hydrogen; and X is a halogen or pseudohalogen, preferably selected from the group consisting of chlorine, bromine, fluorine, iodine, triflate, and nonaflates. While the precise reaction conditions depend on the substrate, in general, a reaction containing about 2 mol% of the catalyst,

about 2 mol% of the ligand, and about 150 mol% of the borane and performed at about 100° to 150° C for about 2 to 20 hours under anhydrous conditions can be expected to produce the arylboronic ester.

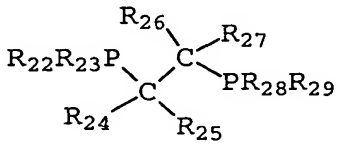
In the second reaction, the C-N bond-forming reaction between the nitrogen of an organic compound comprising a primary or secondary amine and the C-X bond of the arylboronic ester produced above results in the replacement of the halogen with the amine. The reaction is catalyzed by a metal catalytic complex in the presence of a ligand and a base. In a further embodiment, the catalyst comprises palladium. In further embodiments, the base is K_3PO_4, preferably anhydrous K_3PO_4. The second reaction is performed by adding the amine, metal catalytic complex, ligand, and base (optionally, an organic solvent) to the above reaction containing the arylboronic ester, incubating the reaction under anhydrous conditions at a temperature and a time sufficient to produce the aminoarylboronic ester. While the precise reaction conditions depend on the substrate, in general, a reaction containing about 2 mol% of the metal catalyst and about 140 mol% of the base and performed at about 100° C for about 10 to 20 hours under anhydrous conditions can be expected to produce the aminoarylboronic ester.

Effective precatalysts for forming the B-C bonds can be grouped into two families: those that contain cyclopentadienyl (Cp*, C_5R_5 wherein R is CH_3) or indenyl (Ind, C_9R_7 wherein R is H) ligands and those that contain phosphine ligands. Included are

compounds that contain both the Cp* and the Ind ligands and the phosphine ligands.

Preferably, the Ir catalytic composition for the first step of the process comprises one of the following: $(ArH)Ir(BY)_3$ wherein ArH is selected from the group consisting of aromatic, heteroaromatic, polyaromatic, and heteropolyaromatic hydrocarbon and wherein BY is a boron moiety; $(MesH)Ir(BY)_3$ wherein MesH is mesitylene and wherein BY is a boron moiety; $(P(Y_4)(Y_5)(Y_6))_3Ir\ (H)_n(BY)_{3-n}$ wherein Y_4, Y_5, and Y_6 are each selected from the group consisting of hydrogen, halide, alkyl, aryl, alkoxide ($-O(R_{11})$), and amide ($-N(R_{12})(R_{13})$) wherein R_{11}, R_{12}, and R_{13} are each selected from the group consisting of hydrogen, linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, and a carbon in a cyclic structure, wherein n is 0, 1, or 2, and wherein BY is a boron moiety; $(P(R_{14})(R_{15})(R_{16}))_3Ir\ (H)_n(BY)_{3-n}$ wherein R_{14}, R_{15}, and R_{16} are each selected from the group consisting of hydrogen, linear alkyl, branched alkyl, and a carbon in a cyclic structure, wherein n is 0, 1, or 2, and wherein BY is a boron moiety; $(P(Y_4)(Y_5)(Y_6))_3Ir\ (H)(R_{13})(BY)$ wherein Y_4, Y_5, and Y_6 are as above, wherein R_{13} is selected from the group consisting of a linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, aryl, and a carbon in a cyclic structure, and wherein BY is a boron moiety; $(P(R_{14})(R_{15})(R_{16}))_3Ir\ (H)(R_{17})(BY)$ wherein R_{14}, R_{15}, and R_{16} are as above; R_{17} is as above, and wherein BY is a boron moiety; $\{(PY_7P)Ir(BY)_3\}_2(\mu_2\text{-}(PY_7P))$ (**16**) wherein BY is a boron moiety, wherein (PY_7P) is $R_{18}R_{19}P\text{-}Y_7\text{-}PR_{20}R_{21}$ wherein R_{18}, R_{19}, R_{20}, and R_{21}

are each selected from the group consisting of hydrogen, linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, and a carbon in a cyclic structure, and wherein Y_7 is a chain containing 1 to 12 carbons; $(PY_7P)(P(Y_4)(Y_5)(Y_6))Ir(BY)_3$ (**17**) wherein BY is a boron moiety, wherein Y_4, Y_5, and Y_6 are as above, and wherein (PY_7P) is as above; $(PY_7P)(P(R_{10})(R_{11})(R_{12}))Ir(BY)_3$ (**18**) wherein BY is a boron moiety, wherein R_{14}, R_{15}, and R_{16} are as above, wherein (PY_7P) is as above; $\{(P\hat{}P)Ir(BY)_3\}_2(\mu_2\text{-}(P\hat{}P))$ (**19**) wherein BY is a boron moiety and wherein $(P\hat{}P)$ is of the formula

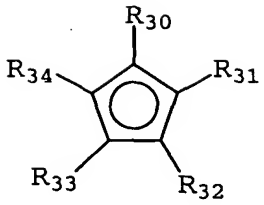


wherein R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each selected from the group consisting of alkyl chains, carbocyclic rings, and aryl groups; $(P\hat{}P)(P(Y_4)(Y_5)(Y_6))Ir(BY)_3$ (**20**) wherein BY is a boron moiety, wherein Y_4, Y_5, and Y_6 are as above, and wherein $(P\hat{}P)$ is as above; $(P\hat{}P)(P(R_{14})(R_{15})(R_{16}))Ir(BY)_3$ (**21**) wherein BY is a boron moiety, wherein R_{14}, R_{15}, and R_{16} are as above, and wherein $(P\hat{}P)$ is as above; $(PY_7P)Ir(BY)_3$ (**22**) wherein BY is a boron moiety, and wherein and (PY_7P) is as above; $(P\hat{}P)Ir(BY)_3$ (**23**) wherein BY is a boron moiety, and wherein $(P\hat{}P)$ is as above; $(P(Y_4)(Y_5)(Y_6))_4Ir(BY)$ wherein Y_4, Y_5, and Y_6 are as above and BY is a boron moiety; $(P(R_{14})(R_{15})(R_{16}))_4Ir(BY)$ wherein R_{14}, R_{15}, and R_{16} are as above and BY is a boron moiety; $(PY_7P)(P(Y_4)(Y_5)(Y_6))_2Ir(BY)$ (**24**) wherein BY is a boron

moiety, wherein Y_4, Y_5, and Y_6 are above, and wherein (PY_7P) is as above; $(P\frown P)(P(Y_4)(Y_5)(Y_6))_2Ir(BY)$ **(25)** wherein BY is a boron moiety, wherein Y_4, Y_5, and Y_6 are as above, and wherein $(P\frown P)$ is as above; $(PY_7P)(P(R_{14})(R_{15})(R_{16}))_2Ir(BY)$ **(26)** wherein BY is a boron moiety, R_{14}, R_{15}, and R_{17} are as above, and wherein (PY_7P) is as above; $(P\frown P)(P(R_{14})(R_{15})(R_{16}))_2Ir(BY)$ **(27)** wherein BY is a boron moiety, wherein R_{14}, R_{15}, and R_{16} are as above, and wherein $(P\frown P)$ is as above.

Examples of catalytic compositions comprising iridium include those selected from the group consisting of $((COD)Ir(OCH_3))_2$, $(Cp^*)Ir(H)_2(Me_3P)$ **(1)**, $(Cp^*)Ir(H)(BPin)(Me_3P)$ **(2)**, $(Cp^*)Ir(H)(C_6H_5)(Me_3P)$ **(3)**, $(Ind)Ir(COD)$ **(8)**, $(MesH)Ir(BPin)(B(OR)_2)$ **(9)**, $((R_1)_3P)_3Ir(B(OR_2)_2)_3$ **(10)**, $(R_1)_2P)_2Ir(BPin)_3$ **(11)**, $(((R_1)_2P)_3Ir((R_2O)_2B)_3)_2$ **(12)**, $((R_1)_3P)_4Ir(BPin)$ **(13)**, $((R_1)_2P)_2Ir(BPin)_3$ **(14)**, $(MesH)Ir(BPin)_3$ (**9** wherein the $B(OR)_2$ is BPin), $IrCl(COD)$ **(15)**, and $(IrCl(COD))_2$, wherein Cp* is 1,2,3,4,5-pentamethylcyclopentadienyl, BPin is pinacolborane, Me is methyl, H is hydrogen, P is phosphorus, Ind is indenyl, COD is 1,5-cyclooctadiene, MesH is mesitylene, and wherein R, R_1, and R_2 are each selected from the group consisting of hydrogen, linear or branched alkyl containing 1 to 8 carbons, aryl, and a carbon in a cyclic structure.

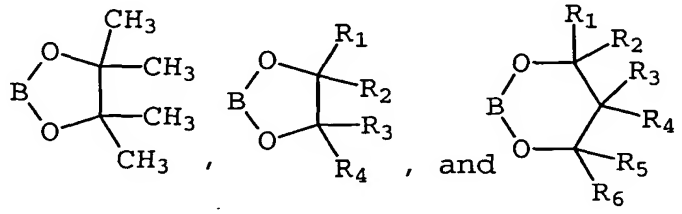
Preferably, the Rh catalytic composition for the first step comprises one of the following: $(Cp')(P(Y_4)(Y_5)(Y_6))Rh(H)_n(BY)_{2-n}$ wherein Y_4, Y_5, and Y_6 are as above, wherein n is 0 or 1, wherein BY is a boron moiety, and wherein Cp' is of the formula



wherein R_{30}, R_{31}, R_{32}, R_{33}, and R_{34} are each selected from the group consisting of hydrogen, alkyl chains, carbocyclic rings, and aryl groups; and $(Cp')(P(R_{14}(R_{15})(R_{16}))Rh(H)_n(BY)_{2-n}$ wherein R_{14}, R_{15}, and R_{16} are as above; n is 0 or 1, wherein BY is a boron moiety; and wherein Cp' is as above.

Examples of catalytic compositions comprising rhodium include those selected from the group consisting of $(Cp^*)Rh(H)_2(Me_3P)$ (**4**), $(Cp^*)Rh(H)(BPin)(Me_3P)$ (**5**), $(Cp^*)Rh(H)(C_6H_5)(Me_3P)$ (**6**), and (Cp*)Rh(hexamethylbenzene) (**7**), wherein Cp* is 1,2,3,4,5-pentamethylcyclopentadienyl, BPin is pinacolborane, Me is methyl, H is hydrogen, and P is phosphorus.

In the above catalytic compositions, preferably the BY boron moiety selected from the group consisting of



wherein R_1, R_2, R_3, R_4, R_5, and R_6 are each selected from the group consisting of hydrogen, linear alkyl containing 1 to 8 carbon atoms, branched alkyl containing 1 to 8 carbons, and a carbon in a cyclic structure. Preferably, the borane is pinacolborane.

Figures 1 and 2 show the structures of precatalysts **1** to **15** and **16** to **27**, respectively.

While the precatalysts can under particular reaction conditions catalyze the borylation of particular ring-substituted arenes, the reactions proceed more efficiently when an organic ligand such as phosphine ligands (phosphorus organic ligands), preferably bidentate phosphine ligands, are included in the reaction mixture. The addition of phosphine ligands to the reaction generates active catalysts which can produce ring-substituted arene boranes (aryl boronate esters and acids) with low catalyst loading. The fact that phosphine-containing species can catalyze borylation is important because numerous phosphines are commercially available. Furthermore, the selectivities of the borylation can be altered as a function of the phosphine ligand that is added. Examples of phosphine ligands include, but are not limited to, trimethyl phosphine (PMe_3), 1,2-bis(dimethylphosphino)ethane (dmpe), 1,2-bis(diphenylphosphino)ethane (dppe), Cy_3P, and Ph_3P. In other embodiments, the ligand can be a nitrogen ligand, preferably a nitrogen ligand selected from the group consisting of 2,2'-dipyridyl and 4,4'-di-tert-butyl-2,2'-dipyridyl.

Examples of catalysts and boron reagents for borylation can be found in commonly owned U.S. Application Serial No. 10/194,809, filed July 12, 2002, and U.S. Application Serial No. 10/194,859, filed July 12, 2002.

Effective catalysts for forming the C-N bond during the amination step of the process are palladium

catalyst complexes. Preferably, the palladium catalytic complexes are selected from the group consisting of $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2(dppf)$, and $Pd(OAc)_2/Cy_3P$ wherein P is phosphorus and Ph is phenyl, dba is dibenzylideneacetone, ^tBu is *tert*-butyl, dppf is diphenylphosphinoferrocene.

The amination reactions proceed more smoothly when a second organic ligand is included in the reaction mixture. Such ligands include, but are not limited to, 2-(N,N'-dimethylamino)-2'-dicyclophosphino-1,1'-biphenyl, tri(*tert*-butyl)phosphine ($PtBu_3$), 2-dicyclohexylphosphino-1,1'-biphenyl, and 2-di-t-butylphosphino-1,1'-bipheyl.

A typical borylation/amination is performed as follows. An anhydrous mixture containing an aryl compound which is a ring-substituted arene having at least one halogen or pseudohalogen such as triflate or nonaflate, a borane such as HBPin, an iridium or rhodium catalytic complex with three or more substituents such as (Ind)Ir(COD), and a organic ligand selected from the group consisting of phosphorus, carbon, nitrogen, oxygen, and sulfur organic ligands such as dpme is placed in a reaction vessel and stirred. The aryl compound to borane molar ratio in particular embodiments can be from about 10 to 1 to 1 to 10, preferably the molar ratio is about 1 to 2. In particular embodiments, the ratio of catalyst to ligand is about 1 to 1. Thus, as an example, in a typical reaction, the aryl compound is about 2 mmol, the borane is about 2 mmol, the catalyst is about 0.04 mmol, and the ligand is about 0.04 mmol. The reaction vessel is preferably sealed and the

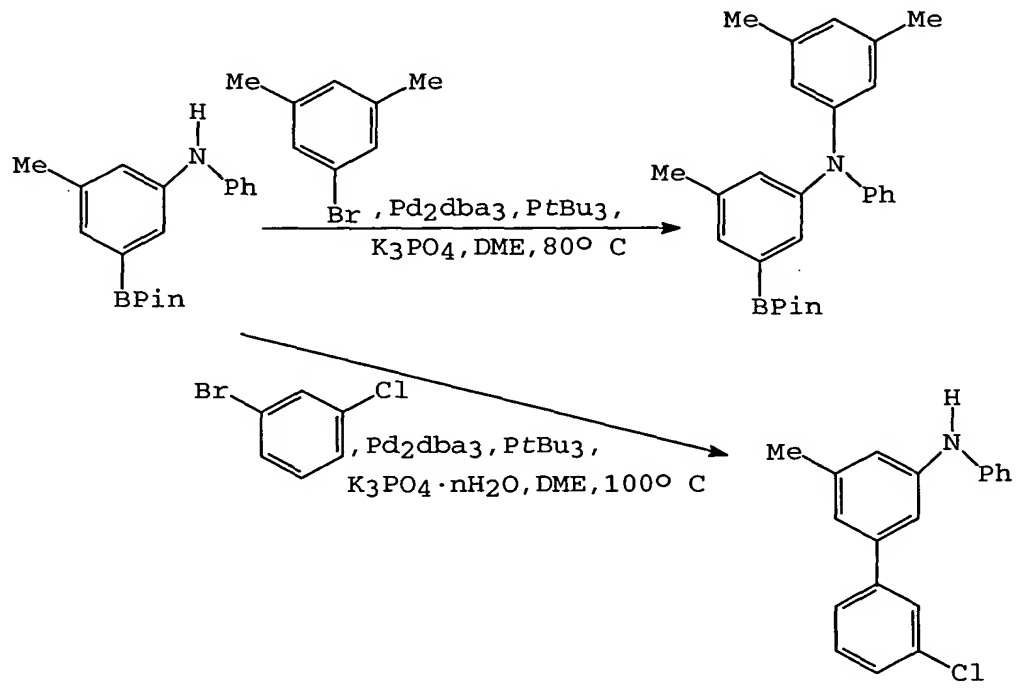
mixture stirred from room temperature to 200° C, preferably about 150° C for a time sufficient to borylate a substantial amount of the aryl compound. Afterwards, the reaction is cooled to room temperature and the reaction then placed under a vacuum for about an hour or passed through a plug of silica.

Next, an organic compound containing an amine moiety, a metal catalyst complex, preferably a Pd catalyst complex such as Pd_2dba_3, a base such as K_3PO_4, a ligand such as $P(t\text{-}Bu)_3$, and a solvent such as DME are added to the above anhydrous reaction mixture containing the arylboronic ester. The reaction is performed under anhydrous conditions. As an example, a typical reaction containing the above example can then include about 0.02 mmol of the catalyst, about 0.06 mmol of the ligand, about 1.4 to 2.8 mmol of the base, and about 2.40 mmol of the amine moiety. The reaction vessel is sealed and the mixture stirred at a temperature between room temperature and 200° C, preferably 100° C, for a time sufficient to aminate a substantial amount of the arylboronic ester. In general, a reaction time between about 16 to 20 hours would be sufficient. Afterwards, the reaction is cooled and the reaction diluted with a solvent such as Et_2O, and then washed with H_2O and dried. The solvents can be removed under reduced pressure and column chromatography can be used to purify the aminoarylboronic ester.

It was furthered discovered that under appropriate conditions, a selective amination (Buchwald-Hartwig amination) or Suzuki coupling of an aminoarylboronic ester can be performed using the same

Pd-catalyst, base, and solvent used to prepare the aminoarylboronic ester. In the presence of water, it was discovered that Suzuki cross-coupling of an aryl halide with the boronic ester occurs exclusively. However, it was also discovered that when the reaction is run under anhydrous conditions, only the amine functionality reacts with the aryl halide. Scheme 1 illustrates the two reactions: the upper reaction is the Buchwald-Hartwig amination reaction and the lower reaction is the Suzuki coupling reaction.

Scheme 1



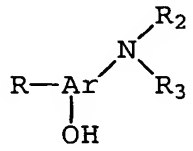
Therefore, once the amino substituted boronic ester has been made via the C-H activation/borylation/amination, that species can be

used in a Pd-mediated Suzuki coupling (C-C bond formation) to make biaryls. Methods for making biaryls from arylboronic esters are disclosed in U.S. Application No. 10/194,859, filed July 12, 2002. Alternatively, the same product can be used in a second Pd-mediated Buchwald-Hartwig amination (C-N bond formation). The key to this divergence is whether the reactions are run in the presence of water (C-C formation) or under anhydrous conditions (C-N formation).

Thus, the present invention further provides a two-step, one-pot process for C-N coupling (Buchwald-Hartwig amination) an aryl halide to an aminoarylboronic ester via the amine functionality of the aminoarylboronic ester by reacting the aminoarylboronic ester with the aryl halide in the presence of a palladium metal catalyst complex under anhydrous conditions and provides a two-step, one pot process for C-C coupling (Suzuki coupling) an aryl halide to an aminoarylboronic ester via the borane functionality of the aminoarylboronic ester by reacting the aminoarylboronic ester with the aryl halide in the presence of a palladium metal catalyst complex in the presence of water.

In a further embodiment of the above Buchwald-Hartwig or Suzuki processes, the palladium catalyst complex is selected from the group consisting of $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2(dppf)$, and $Pd(OAc)_2/Cy_3P$ wherein P is phosphorus and Ph is phenyl, dba is dibenzylideneacetone, ^tBu is *tert*-butyl, dppf is diphenylphosphinoferrocene.

In further embodiments of the present invention, the above aminoarylboronic esters can be oxidized to a substituted phenol amine of the general formula



wherein R, R_2, and R_3 are each independently an alkyl, aryl, vinyl, alkoxy, carboxylic esters, amides, or halogen and Ar is any variety of phenyl, naphthyl, anthracyl, and heteroaryl. The aminoarylboronic ester produced as above is incubated in the presence of an oxidizing compound such as an alkali metal peroxymonosulfate, preferably potassium peroxymonosulfate, most preferably, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ or OXONE (the trademark OXONE is owned by E.I. du Pont de Nemours and Company, Wilmington, Delaware), to remove the boronic ester group as shown in Example 4 to produce the substituted phenol amines. Alternatively, the boronic ester group can be replaced by hydrogen. Methods for oxidizing arylboronic esters to substituted phenols are described in U.S. Provisional Patent Application No. 60/397,366, which was filed July 19, 2002. These methods can be used to oxidize aminoarylboronic esters to substituted phenol amines. Other oxidizing compounds include a peroxy compound selected from the group consisting of peroxymonosulfuric acid and salts thereof; organic peroxides and salts thereof such as hydrogen peroxide.

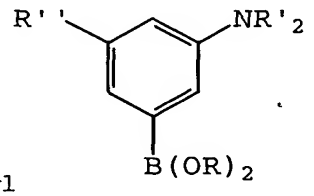
The following examples are intended to

promote a further understanding of the present invention.

EXAMPLE 1

This example illustrates the tandem Ir-catalyzed borylation and catalytic amination process.

3-Aminoboronic acids and esters as shown below are of interest as evidenced by the large number of derivatives synthesized, and by several patents, which note their activity as O-lactamase inhibitors (See, for example, Shoichet et al., WO0035905).



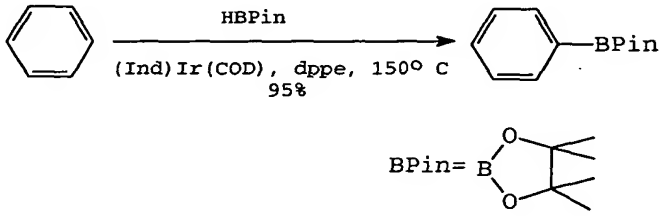
R=H, alkyl, aryl
R'=H, alkyl, aryl, carboxy
R''=H, halo, alkyl, aryl, alkenyl, alkoxy, carboxy, etc.

Few in number, however, are 1, 3, 5-aminoboronic acids and esters (about 25 compounds by SCIFINDER SCHOLAR). Such substrates may prove useful for further derivatization as they can possess three unique sites for diversity. Furthermore, these compounds may prove ideal as scaffolds for combinatorial libraries. The boronic acid or ester can be transformed into a myriad of functionalities including aryl or vinyl via the Suzuki-Miyuara coupling (Miyaura and Suzuki, Chem. Rev. 95: 2457-2483 (1995); Suzuki, J. Organomet. Chem. 576: 147-168 (1999); Miyaura, In Advances in Metal-Organic Chemistry: Liebeskind, Ed.: JAI: London,; Vol. 6, pp.

187-243 (1998)). If R`` is a halogen, then there exists a multitude of coupling opportunities (See, for examples, Metal-catalyzed Cross-coupling Reactions; Diederich and Stang, eds.: Wiley: Wienheim, 1998).

Recently, a catalytic aromatic C-H activation/borylation reaction utilizing Ir- or Rh-catalysts was developed. The process is high yielding, functional group tolerant (alkyl, halo, carboxy, alkoxy, and protected amino), chemoselective (1,3-substited arenes give only the 5-boryl product), and efficient (Iverson and Smith, J. Am. Chem. Soc. 121: 7696-7697 (1999); Cho et al., J. Am. Chem. Soc. 122: 12868-12869 (2000); Tse et al., Org. Lett. 3: 2831 (2001); Chao et al., Science 295: 305-308 (2002)). Furthermore, the process allows for the direct construction of aryl boronic esters from hydrocarbon feedstocks without going through an aryl halide. Scheme 2 depicts a prototypical borylation reaction: borylation of benzene using (Ind)Ir(COD) (2 mol %), dppe (2 mol%).

Scheme 2



The borane of choice is pinacolborane (HBPin). A variety of Ir(I) catalysts can be used, including $[Ir(COD)Cl]_2$, $Ir(Indenyl)(C_2H_4)_2$, Ir(Indenyl)dppe, and (Indenyl)Ir(COD), in the presence of 2 mol equivalents of PMe_3 or 1 mol equivalent of a

bidentate ligand like dmpe or dppe. The catalyst system of choice is (Indenyl)Ir(COD), dppe or dmpe (2 mol% each) because of it's cleanness of reaction and efficient TOF (24 h^{-1} with benzene). The reaction can be run in the neat arene or in inert solvents (e.g. cyclohexane). During our studies into tandem borylation/Suzuki coupling, we noted difficulties with the hydrolysis of the boronic ester functionality (Bpin). The robustness of the BPin group suggested that, perhaps, the pinacol might serve as a protecting group for the boron. Thus, it was deemed of interest to explore other catalytic transformations in the presence of the BPin group. One such transformation is the Buchwald-Hartwig amination of aryl halides (See, for example; Wolfe et al.,. J. Org. Chem. 65: 1158 (2000); Hartwig et al., J. Org. Chem. 64: 5575 (1999); Wolfe and Buchwald, Angew. Chem. Int. Ed. 38: 2413 (1999)). Initially, the reaction was attempted on pure 1-chloro-3-methylphenyl-5-BPin. As shown in Scheme 3 (Buchwald-Hartwig coupling of 1-chloro-3-methylphenyl-5-BPin with aniline), application of Buchwald's protocol proceeded cleanly to give the desired cross-coupling product in 64.7% and 63.8% yield. The use of $PtBu_3$ improved the yield to 78.8%. Unfortunately, initial attempts to perform the reaction in the "one-pot" protocol were unsuccessful. Table 1 summarizes the results. In all cases where $K_3PO_4 \cdot nH_2O$ was used, a significant amount of pinacol was observed by GC-FID (Entries 1-5). While this is indicative of reaction of the BPin group and is most likely a by-product of Suzuki coupling (in this case,

dimerization or oligiomerization of the starting material), no dimers or oligiomers were isolated.

Scheme 3

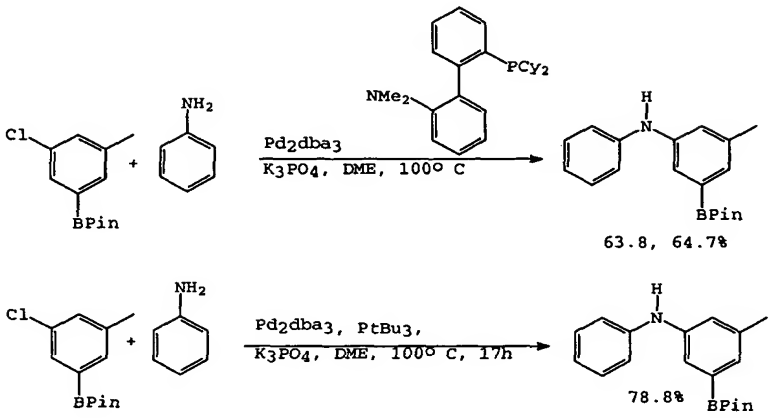
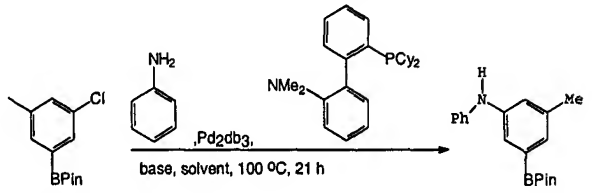
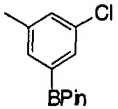
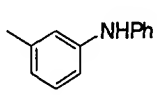
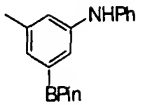


Table 1.
Attempted Buchwald-Hartwig amination of 3-chlorotoluene in tandem catalysis.[a]

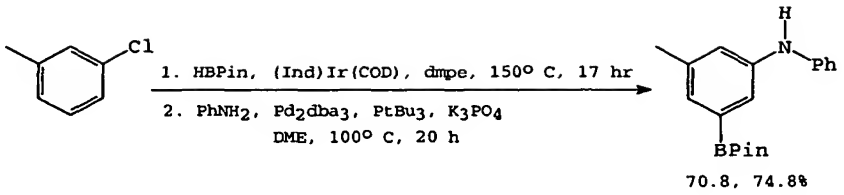


Entry	Mol% Pd Catalyst	Mol% Ligand[e]	Base	H_2NPh	Pinacol				
1	1.0	4.0	$K_3PO_4 \cdot nH_2O$	70	27	trace	trace	3	o
2	0.5	3.0	$K_3PO_4 \cdot nH_2O$	69	20	6	0	5	o
3	1.0	4.0	$K_3PO_4 \cdot nH_2O$	58	14	19	4	5	o
4	2.0	6.0 $PfBu_3$	$K_3PO_4 \cdot nH_2O$	58	15	0	6	11	10
5[b]	0.5	2.0	$K_3PO_4 \cdot nH_2O$	65.5	25.5	0	0	9	0
6[c]	0.5	2.0	K_3PO_4	35	0	35	4	3	23
7[d]	1.0	4.0	KO*t*Bu	38	0	32	2	19	9
8	2.0	8.0	K_3PO_4	51	0	17	21	3	8
9	2.0[d]	8.0	K_3PO_4	45	0	53	2	0	trace
10[f]	1.0	3.0	K_3PO_4	36	0	8	17	-	39

[a]Crude ArBPin: obtained from 3-chlorotoluene, 1.5 eq. HBPin, 0.02 eq. (Ind)Ir(COD), 0.02 eq. dppe and was used w/o further purification. Unless otherwise noted, reactions were run with 1.4 eq. base and in DME with 1.2 eq. aniline. [b]Crude ArBPin passed through a plug of silica prior to use. [c]Reaction was run for 2 days. [d]Reaction run in THF. [e]Ligand was 2-(N,N-dimethylamino)-2'-diphenylphosphino-1,1'-biphenyl. [f]Run for 4 days. Isolated 34.4% of desired product.

Noteworthy, is the formation of the desired product, albeit in low yield (10% GC-FID ratio), using $K_3PO_4 \cdot nH_2O$ and P*t*Bu$_3$ when all other attempts using the base failed. With anhydrous K_3PO_4, results were better (Entries 6-9). Most importantly, no pinacol was formed in these reactions. Changing the base or increasing catalyst loading did not improve the results. The use of P*t*Bu$_3$ led to the best results and after 4 days at 100°C, 34.4% of the desired product was isolated (Entry 10). This result, however, falls short of the reaction performed on pure material and shows that the by-products from the Ir-catalyzed borylation are not completely innocuous. As was previously mentioned, a potential source of concern is the presence of free bidentate phosphines after the borylation, which may interfere with subsequent reactions. In the tandem Suzuki reactions, an aryl chloride was successfully coupled only when dmpe was used as the Ir ligand. Thus, the tandem borylation/Buchwald-Hartwig amination reaction of the present invention was attempted using the (Ind)Ir(COD)/dmpe precatalyst. Gratifyingly, this protocol gave the desired aminoaryl boronic ester is an overall yield of 70.8% and 74.8% from 3-chlorotoluene. This one-pot borylation/Buchwald-Hartwig amination process of the present invention is shown in Scheme 4.

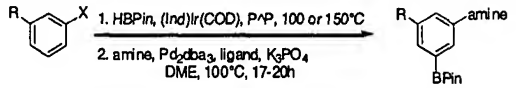
Scheme 4

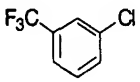
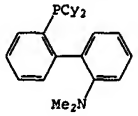
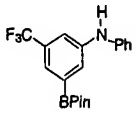
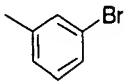
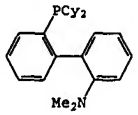
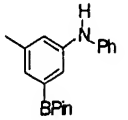
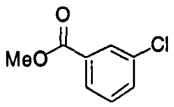
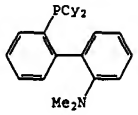
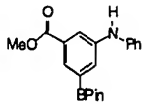
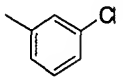
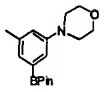
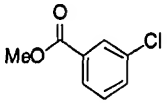
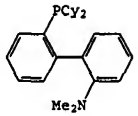
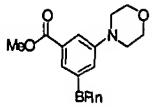
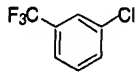
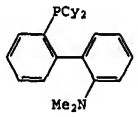
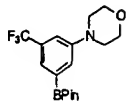


70.8, 74.8%

Again, it was preferable to run the reaction under anhydrous conditions to substantially avoid Suzuki coupling. If one performs the reaction in a stepwise fashion, the overall yield is 60.1%. Thus, it appears that the tandem approach affords the product in significantly better yield. A series of substrates and amines were subjected to the tandem borylation/Buchwald-Hartwig (B-H) amination protocol of the present invention, as shown in Table 2.

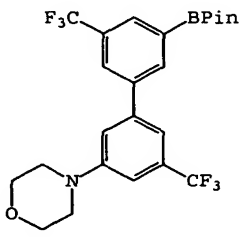
Table 2
Buchwald-Hartwig amination in tandem catalysis.[a]



Entry	Substrate	Ir P ligand	Amine	Pd P ligand	Product	% yield
1		dppe	$PhNH_2$			71 66.5 69.7[b]
2		dppe	$PhNH_2$			46.9 47.6
3		dppe	$PhNH_2$			47.4
4		dmpe	morpholine	$PtBu_3$		73.4
5[c]		dppe	morpholine			43.2
6[c]		dppe	morpholine			46.3 48.9

[a]All borylations: 150 mol% HBPin, 2 mol % (Ind)Ir(COD), 2 mol% bidentate phosphine. All aminations: 2 mol% Pd_2dba_3, 140 mol% K_3PO_4, DME at 100 °C for 16-20 hours. [b]$PtBu_3$ was used. [c]Small amounts of aminated dimers were detected.

Thus, both electron-rich and electron-poor haloaryl boronic esters can be aminated in moderate to good yields using this protocol. Thus, for example, borylation of 3-chlorotoluene followed by amination with morpholine using Pd_2dba_3 and $PtBu_3$ gives the desired aminoaryl boronic ester in 73.4% yield. Borylation of 3-trifluoromethyl toluene followed by amination with aniline using Pd_2dba_3 with either the Buchwald biaryl phosphine or Hartwig $PtBu_3$ ligand also gives the corresponding aminoaryl boronic ester in good yield (Entry 1; 68.7% for the former and 69.7% for the latter). Contrariwise, amination of the same aryl boronic ester with morpholine was not as successful (Entry 6; 47.6%). For this reaction, a compound (GC-FID ratio to product is 7.7 to 92.3) tentatively identified by GC-MS and ^1H NMR as the aminated dimer was isolated. The structure of the aminated dimer is



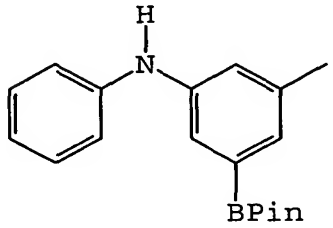
The aminated dimmer is believed to be the result of amine induced Suzuki coupling of the aryl boronic ester with another molecule of itself followed by Pd-catalyzed amination of the remaining chloride group. A similar dimerization was observed for Entry 5 and is presumably formed in a similar manner. As the initialdimer is bifunctional (i.e., it has a chloro and a BPin group), further oligiomerization is likely

and thus may account for the poor yield in these cases. The Suzuki coupling is facilitated by electron-poor aryl boronic esters (Entries 1, 3, 5, 6), which will activate the boron towards nucleophilic attack by a base and by a stronger base [protonated pK_a (morpholine) = 8.36; pK_a (aniline) = 0.78] (Entries 4-6). It is, therefore, likely that the low yields in Table 2 are attributable to competing Suzuki oligiomerization. The successful tandem reaction using (Ind)Ir(COD), dppe for borylation for Entry 1 was somewhat unexpected. Recall that for 3-chlorotoluene, the use of dppe inhibited the subsequent amination. It may simply be that the more activated aryl halides are readily aminated and do not require highly active Pd-catalysts.

While this coupling is remarkable, the usefulness of the products for further transformations could be called in question. In particular, could the boronic ester functionality be coupled to give an aminobiaryl (Scheme 1, lower reaction) or would the amine undergo Buchwald-Hartwig amination to give a trisubstituted amine (Scheme 1, upper reaction). To address this issue, pure 1-N-phenyl-3-methylphenylboronic ester was subjected to coupling with 3-chlorobromobenzene. Gratifyingly, the desired biaryl was obtained in 69% yield. In addition to the selectivity of the coupling, the product would not be easily accessible following an alternative route; namely, Suzuki coupling followed by amination because there would be an issue as to which chloro group would be functionalized.

EXAMPLE 2

Tandem Synthesis of N-phenyl-3-BPin-5-methylaniline.



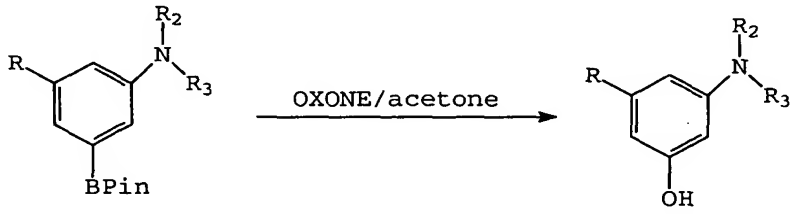
To an airfree flask equipped with a stir bar, in a glove box, was added 3-chlorotoluene (253 mg, 2.00 mmol), HBPin (512 mg, 4.00 mmol), (Ind)Ir(COD) (16.6 mg, 0.04 mmol), dmpe (6.0 mg, 0.04 mmol). The flask was sealed, removed for the glove box, and stirred at 150 °C for 17 h. The reaction mixture was allowed to cool to room temperature and subsequently placed under vacuum for ~1h. The air free flask was brought into the dry box and Pd_2dba_3 (18.3 mg, 0.02 mmol), $P(t\text{-}Bu)_3$ (12.1 mg, 0.06 mmol), K_3PO_4 (594 mg, 2.8 mmol), aniline (224 mg, 2.41 mmol), and DME (3 mL) were added. Sealed, removed from dry box, and stirred at 100 °C for 19h. Cooled, diluted with Et_2O, washed with H_2O (3 x 30 ml), dried with $MgSO_4$, and removed solvents under reduced pressure. Column chromatography eluting with hexanes:CH_2Cl_2 (2:3) gave 462.8 mg (74.8%) of the desired product as a light yellow oil. mp = 100 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, J = 2.0 Hz, 1H), 7.56 (br s, 1H), 7.07-7.03 (m, 2H), 6.92-6.89 (m, 2H), 6.86 (br s, 1H), 6.77-6.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.0, 143.0, 138.4, 129.5, 129.1, 122.4,

122.2, 120.7, 117.8, 83.66, 24.94, 21.34. ^{11}B NMR (C_6D_6, 96 Hz) δ 29.12. FT-IR (NaCl) 3393, 3365 (sh), 3036, 2979, 2926, 2867, 1590, 1518, 1497, 1470, 1410, 1368, 1312, 1271, 1237, 1215, 1167, 1144, 1117, 1031, 1019, 967, 911, 853, 745, 712, 698, 668 cm^{-1}. GC-MS retention time = 17.94 min. MS (% rel. int.): *m/z* 309 (100), 294 (2), 250 (3), 236 (7), 209 (27), 193 (14), 167 (11), 147 (5). Anal. Calcd for $C_{19}H_{24}BO_2N$: C, 73.80; H, 7.82; N, 4.53. Found: C, 73.82; H, 7.94; N, 4.43.

EXAMPLE 3

A process for producing substituted phenol amines from aminoarylboronic esters is provided.

An aminoarylboronic ester is prepared as in any one of the above examples and then oxidized to its corresponding phenol using one of the four conditions shown below.



Oxidation condition A is as follows. A mixture prepared as above containing the aminoarylboronic ester is placed in an air free flask and is vigorously stirred. To this mixture is added 1.5 mL 1.5 M aqueous NaOH, followed by 5 min stirring. Then 0.73 g $NaHCO_3$ is added followed by 4.7 ml acetone. The mixture is cooled by an ice bath, and 3.2 mL 0.33 M aqueous OXONE is added slowly. After 12-15 min of stirring, the reaction is quenched by $NaHSO_3$.

Oxidation condition B (no $NaHCO_3$) is as follows. A mixture prepared as above containing the aminoarylboronic ester is placed in an air free flask and is vigorously stirred. To this mixture is added 1.5 mL 1.5 M aqueous NaOH, followed by 5 min stirring. Then 4.7 ml acetone is added. The mixture is then cooled by an ice bath, and 3.2 mL 0.33 M aqueous OXONE is added slowly. After 12-15 min of stirring, the reaction is quenched by $NaHSO_3$.

Oxidation condition C (no NaOH) is as follows. A mixture prepared as above containing the aminoarylboronic ester is placed in an air free flask and is vigorously stirred. To this mixture is added 3.0-3.5 ml acetone and 3-5 min are allowed to stir. The mixture is then cooled by an ice bath, and 3.2 mL 0.33 M aqueous OXONE is added slowly. After 12-15 min of stirring, the reaction is quenched by $NaHSO_3$.

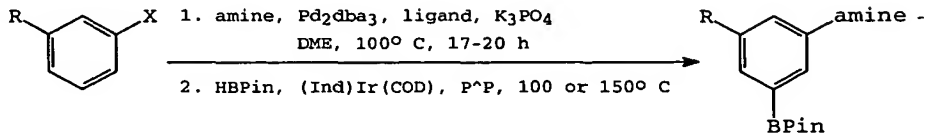
Oxidation condition D (no ice bath) is as follows. A mixture prepared as above containing the aminoarylboronic ester is placed in an air free flask and is vigorously stirred. To this mixture is added 3.0-3.5 ml acetone and 3-5 min are allowed to stir. Then 3.2 mL 0.33 M aqueous OXONE is added dropwise at room temperature. After 7 min of stirring, the reaction is quenched by $NaHSO_3$.

In the oxidation, the preferred acetone/water ratio is about 1:1. While other solvents can be used in the oxidation, acetone is presently the preferred solvent. The phenol can be prepared by column chromatography or sublimation.

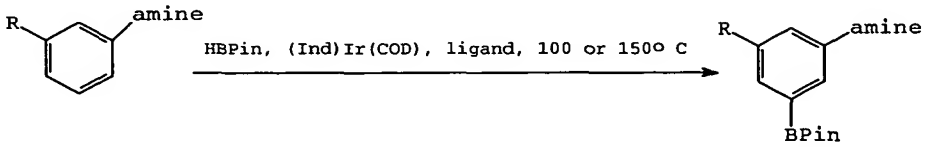
EXAMPLE 4

Alternative process for producing aminoarylboronic acids and esters, which are more lengthy or more limited in scope. Below are two such processes (Schemes 5 and 6):

Scheme 5



Scheme 6



For primary amines and arylamines, borylation may in some cases prove problematic. For other amines, borylation may in some cases proceed very slowly. Therefore, the above processes are possible as well.

While the present invention is described herein with reference to illustrated embodiments, it should be understood that the invention is not limited hereto. Those having ordinary skill in the art and access to the teachings herein will recognize additional modifications and embodiments within the scope thereof. Therefore, the present invention is limited only by the claims attached herein.